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LITHIUM DIISOPROPYLAMIDE (LDA) AS AN EFFICIENT REDUCING AGENT FOR THIOKETONES - MECHANISTIC CONSIDERATION

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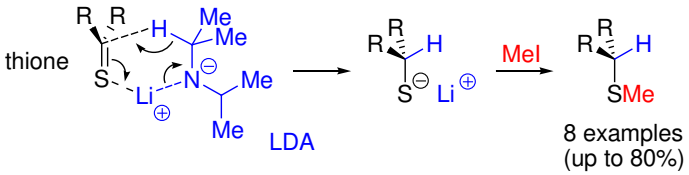
GRAPHICAL ABSTRACT



Abstract *Treatment of thiocarbonyl compounds with excess LDA leads to the corresponding thiols or sulfides depending on the work-up procedure. The mechanistic scenario for this unusual reduction pathway is discussed.*

Keywords thioketones; LDA; hydride transfer; sulfides; reaction mechanisms

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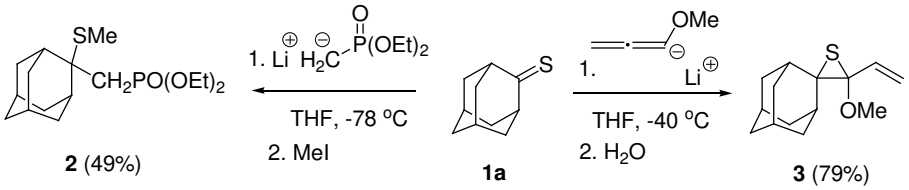
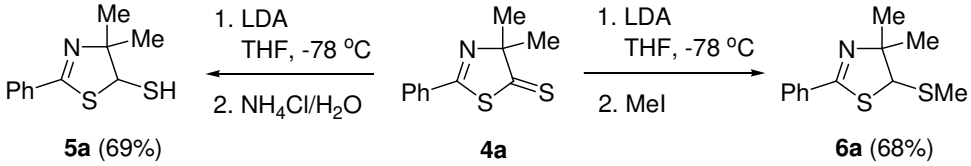
INTRODUCTION

Thioketones belong to the class of reactive dipolarophiles (so-called superdipolarphiles) widely applied for the synthesis of numerous *S*-heterocylic systems.[1] However, their behavior towards lithiated agents is by far less well known. As a part of our ongoing project focused on the exploration of thioketones in organic, materials, coordination, and biometaloorganic chemistry,[2] a series of model compounds of type **1** was recently shown to be suitable reaction partners in reactions with *C*-nucleophiles. For example, treatment of adamantanethione (**1a**) with lithiated methylphosphonate followed by methyl iodide or with methoxyallene anion provided the corresponding products, i.e., the phosphonylated sulfide **2**[3] and vinylthiirane derivative **3**,[4] respectively, as the result of exclusive *carbophilic* attack onto the C=S group (Scheme 1).



Scheme 1 Reactions of adamantanethione (**1a**) with lithiated *C*-nucleophiles.

Within the studies on [3+2]-cycloadditions of thioketones with azomethine ylides, 1,3-thiazole-5(4*H*)-thione **4a** was selected as a model compound.[5] Unexpectedly, the treatment of a mixture of **4a** and trimethylamine oxide, used as the anticipated source of the parent azomethine ylide,[6] with LDA at 0 °C provided only the reduction product **5a**. Further experiments with **4a** confirmed the unusual potential of LDA for the reduction of the C=S group. Thus, depending on the work-up procedure, the corresponding thiol **5a** or methylsulfide **6a** were obtained in high yields[7] (Scheme 2).



Scheme 2 Reduction of 1,3-thiazole-5(4*H*)-thione **4a** with LDA.

RESULTS AND DISCUSSION

Following the protocol established for compound **4a**, a spirocyclic 1,3-thiazole-5(4*H*)-thione of type **4** and a series of thioketones **1** were smoothly reduced with excess of LDA to give the respective thiolates, which after trapping with methyl iodide as the electrophile provided the expected products **6b** and **7a-f**, respectively, in high yields (Figure 1). Analytically pure samples of products were obtained after chromatographic purification in 40–80% yields. Hence, as shown in Figure 1, dithioacetals **6a**-**b**, as well as cycloaliphatic (**7a**-**b**) and aromatic (**7c**-**f**) sulfides including unique diferrocenyl (**7e**) and hetaryl (**7f**) derivatives are available by the presented method, though the yields in the latter cases are rather low.[7]

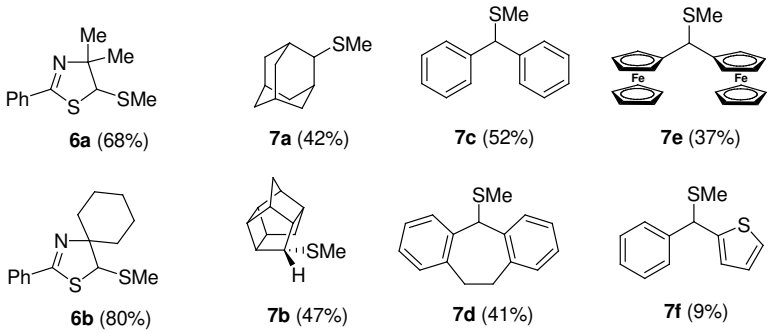
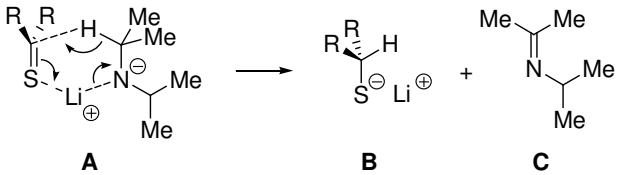


Figure 1 Products **6** and **7** prepared by the reduction of the respective thiocarbonyl substrates.

Although lithium amides are known in the first line as a strong bases, often used for the deprotonation of CH-acidic compounds, reducing properties of LDA and its analogs have also been reported.[8] For example, LDA-induced conversion of nitroarenes to the corresponding aromatic amines and azoxyarenes via a single electron transfer (SET) mechanism was described.[8a] An analogous reaction pathway was postulated for the observed formation of sulfides from 2,2-diaryl-1,3-dithiolanes via the in situ generated aromatic thioketones.[8b] On the other hand, treatment of 4-fluorotoluene with LDA in diethyl ether gave, among other products, a mixture of *meta*- and *para*-ethyl(2-tolylethyl)amine.[9a] A reaction mechanism via hydride transfer from $LiNEt_2$ to the intermediate aryne and subsequent addition of the aryl anion to the formed imine was proposed. Furthermore, the reduction of benzophenone with $LiNEt_2$ was interpreted as a hydride-transfer reaction via a six-membered transition state.[9b] A strong evidence for this reaction mechanism are enantioselective reductions of ketones with enantiomerically pure lithium alkyl phenyl amides[9c] and lithium dialkylamides.[9d] This pathway resembles that of reactions of Grignard reagents with sterically demanding carbonyl compounds as well as Meerwein-Schmidt-Ponndorf-Verley reductions of ketones.[10]



Scheme 3 Postulated transition state (**A**) and hydride shift leading to thiolate **B**.

Based on the reports discussed above we suggest, that LDA in the reaction with non-enolizable thioketones acts as a hydride donor. Hydride transfer via the 6-membered

transition state **A** leads then to thiolate **B**, which can be protonated or trapped with appropriate electrophiles. The respective imine **C** is formed as a side-product (Scheme 3).[11] However, the competitive SET mechanism, especially in the case of hetaryl substituted thioketone **1f**, can't be ruled out.

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[11] A small amount of the imine **C** was identified in the ^{1}H NMR spectra of crude mixtures obtained with both adamantanthione (**1a**) and thiobenzophenone (**1c**); a characteristic septet attributed to the C*H*Me$_2$ group was found at 3.77 ppm.[12] In addition, no incorporation of a deuterium atom was observed, when the reaction of LDA with **4a** was performed in THF-d_8.[7]

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